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TITLE: A Population-Based Randomized Trial to Assess the Effects of Short-Term Cessation of Hormone Replacement Therapy on Mammography Assessments and Breast Density

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14. ABSTRACT
This randomized controlled trial was designed to test whether short-term (1-2 months) hormone replacement therapy (HRT) cessation will sufficiently lower breast density to decrease the proportion of women who receive a recommendation for additional evaluation following a screening mammogram, and to examine whether there is a trend in decreased recall by duration of HRT cessation. The study was conducted at Group Health, a managed health care organization with an organized breast cancer screening program. We sought to recruit 1,500 women to be randomized to one of three HRT arms: 1) cessation two months before the screening mammogram, 2) cessation one month before, and 3) continued HRT use. We measured breast density using a computer-assisted method and mammography recall rates from an expert radiologist review of the mammograms; both readers were blinded to HRT status. Recruitment started 11/2004 and ran through 9/30/2007, we contacted 5,861 potentially eligible women. Among those, we consented, enrolled and randomized 1704 (29.1%) women. Of the remaining 4,157 (70.9%); 977 (16.7%) were ineligible, we were unable to contact 179 (3.1%) and 2 (<0.1%) have an unknown reason.

15. SUBJECT TERMS
Randomized controlled trial, Mammography, Health care setting, hormone replacement therapy, Breast Density

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INTRODUCTION:

This randomized controlled trial was designed to test whether short-term (1-2 months) hormone replacement therapy (HRT) cessation will sufficiently lower breast density to decrease the proportion of women who receive a recommendation for additional evaluation following a screening mammogram, and to examine whether there is a trend in recall by duration of HRT cessation. The study was conducted at Group Health Cooperative, a managed health care organization with an organized breast cancer screening program. We used automated data to identify HRT users who were due to have their next screening mammograms. Women were recruited through mailed correspondence and telephone contact. We sought to recruit 1,500 women to randomize to one of three HRT arms: 1) cessation two months before the screening mammogram, 2) cessation one month before, and 3) continued HRT use. We measured breast density using a computer-assisted method. Mammography recall rates were being determined from an expert radiologist review of the mammograms. Both readers were blinded to HRT status. We tested whether: 1) HRT cessation 1 or 2 months before a screening mammogram reduced the likelihood of receiving a recommendation for additional evaluation (recall) compared to women who continue using HRT; 2) HRT cessation for 1 versus 2 months affected the likelihood of receiving a recommendation for additional evaluation; and 3) whether there is a greater change in breast density (to lower breast density) among women who stop HRT 1 or 2 months before a screening mammogram to those who do not stop HRT. Change in breast density was measured as the difference between breast density on the screening mammogram before the trial (while on HRT) and on the mammogram during the trial. As part of this trial we also evaluated: 1) women's tolerance (defined as continued cessation) for short-term (1-2 months) HRT cessation, 2) the rate of HRT re-initiation after participation in the trial, and 3) rates of reported adverse events (return of hot flashes, thromboembolic events within the first 6-months after re-initiation, and return of bleeding with re-initiation among previously amenorrheic women) across randomization groups.

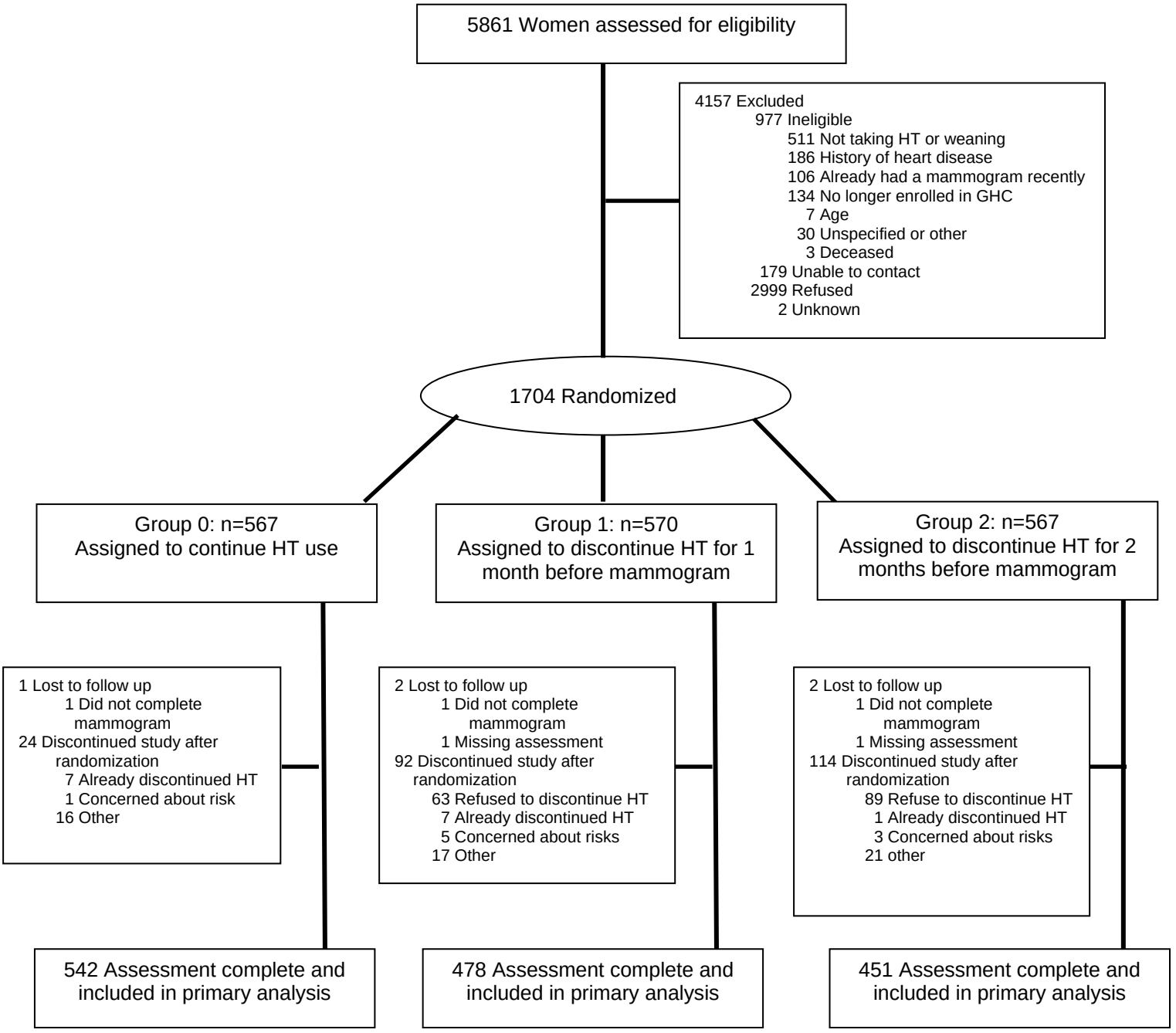
BODY:

Progress on the scope of work (SOW) outlined in the original proposal.

Task A. Recruit 1500 women to participate in the trial

Study recruitment began in November 2004, after final Human Subjects Research Review Board (HSRRB) approval. We completed recruitment in September 2007: Figure 1 outlines the recruitment flow.

Figure 1: READ study recruitment



In our original proposal, we estimated an enrollment of 21.9% of the women approached. We were above target by recruiting 29.1% of women approached. The pool of potentially eligible women declined in the wake of the report of adverse effects of hormone therapy from the Women's Health Initiative in July 2002 and HRT use decreased among members of GHC to less than 30% of the levels in 2001. The number of potentially eligible women dropped each month during recruitment and we approached everyone eligible. More than 10% (13.5%) of randomized women withdrew after randomization with nearly all the withdrawal occurring before study mammogram. Withdrawal was differential across groups; 4.2% no cessation, 15.6% 1-month cessation and 20.1% 2-months cessation. Reasons for withdrawal were varied, but the large proportion of women in the cessation group (68.5%-78.1%) withdrew because they refused to discontinue HT after receiving their randomization assignment.

With the supplemental funds awarded in 2006, we extended recruiting for 15 months beyond the original end date for recruiting of 5/31/2006 and were able to meet our recruitment goal.

Of the 1704 women recruited, 231 (13.6%) women withdrew from the study before completing all study activities leaving 1473 women who were randomized and completed all study activities.

Women were block randomized based on their BI-RADS breast density category at index mammogram and type of HT used in the previous six months before recruitment based on electronic records of pharmacy dispensings (EPT vs. ET) to one of the three study groups: no cessation, 1-month cessation, or 2-month cessation. All women were mailed a personalized letter informing them which study group they were randomized to, a baseline questionnaire and personalized study instructions specific to their randomization group. The instructions also included the participant's mammogram appointment date and for those in the cessation groups the date they should stop their HT. Study participants were provided a toll-free number they could call to speak with the study nurse about any concerns related to the study and to report symptoms and any adverse events.

The study nurse contacted women randomized to the cessation arms approximately two weeks before their scheduled HT cessation date during which she reviewed the HT cessation details, answered questions, and confirmed that that the baseline questionnaire had been completed and returned. She contacted all women randomized to the continuation arm approximately one month before their scheduled mammograms, confirmed their mammogram appointment time and confirmed that their baseline questionnaire had been returned.

The mean age was 58.7 years, mean BMI 27.1 kg/m^2 and 91.4% of the study population was Caucasian. There were no differences (p-values) in age (0.75), BMI (0.79), race (0.79) ethnicity (0.12), education (0.48), and breast cancer risk (0.31) across groups. The majority of the study population (>60%) used unopposed estrogen. Nearly half of the study population had tried to quit HT at some time previously. Approximately one-third of the women self-reported having hypertension, high cholesterol and/or depression.

Task B. Develop Study Materials

The study staff developed study materials and received approval for all materials from the GHC HSRC and the HSRRB. Study staff met with the Advisory board members at least once a year to review recruitment, strategize about increasing recruitment, to review blinded Data Safety and Monitoring Board reports, for a final meeting to review the final recruitment information and to thank them for their contribution to the success of this study.

We collected self-reported information from women at four time points: breast cancer risk factor data from the Group Health mammography questionnaire at the index and study mammogram; baseline study questionnaire data at randomization, and follow-up study questionnaire information at the time of the study mammogram (after HT cessation and just before the study mammogram).

The baseline survey included questions about HT use, menopausal symptoms including sleep, mood swings, vaginal bleeding, vaginal dryness, hot flashes and night sweats), medical history, physical activity, tobacco and alcohol use. The follow-up survey administered before the scheduled mammogram asked specifically about HT cessation compliance, tolerance to HT cessation, menopausal symptoms, and specific adverse events. Body mass index (BMI) was collected at the time of each mammogram; the "pre-study BMI" was collected at the time of the pre-study mammogram.

On both surveys, participants evaluated their general symptoms, night sweats, and hot flashes during the preceding one-month time period, and evaluated their sleeping problems over the preceding one-week period. We also collected symptom information reported on the study hotline. We used a modified Wiklund Menopause Symptom Checklist to ascertain the rate and severity of general menopausal symptoms on a scale from 0 (not present) to 10 (severe). Participants use a scale of 1 (not important) to 10 (very important) to rate the importance of getting a good night's sleep. All other questions assessing sleep asked how often a particular sleep problem occurred, from 0 (never) to 7 (daily). A positive change indicated an increase in symptom severity and sleep disturbances between randomization and study mammogram.

Task C. Monitor the safety of HRT cessation and initiation

The Study Nurse collected information on all adverse events identified from self-report, the study toll free phone number, or automated administrative data. The study team followed all procedures for reporting Adverse Events to GHC HSRC and DOD HSRRB. The programmer reviewed automated administrative data each month to extract information on women enrolled in the study to identify adverse events noted in in-patient and out-patient procedures using ICD-9 and CPT codes. The study physician and study monitor have reviewed all adverse events identified from self-report, the study toll free phone number, and automated administrative data for an assessment of the relation of the event to study participation.

The study biostatistician generated and distributed one Data Safety and Monitoring Board report to the DSMB. The Data Safety Monitoring Board met once during this period (April 1, 2008) to review final study recruitment and safety information. During the course of the study the DSMB met 5 times, 10/22/03, 11/8/05, 6/27/06, 5/29/07 and the final meeting 4/1/08. At each meeting the DSMB reviewed the report and recommended no changes to study procedures. Data safety and monitoring activities will continue through January 2009 in compliance with the provisions of the original grant that specifies following up for adverse events for 1 year after the study mammogram..

1469 women returned a follow-up questionnaire that includes questions on their intention for restarting HRT and compliance with HRT cessation during the study. The questionnaire was mailed to women two weeks before their mammogram appointment.

There were eight serious adverse events among the 1704 randomized participants (through 3/17/08); 2 myocardial infarctions (both in continued use), 2 strokes (1 continued use, 1 1-month cessation) and 4 deaths (2 continued use, 1 1-month cessation, 1 2-month cessation). The continued use group had the greatest number of adverse events reported among women including: 3 breast cancers, 2 atypical chest pain, 3 vaginal bleeding, and 8 other events (e.g., fracture/fall, laceration). One woman in the 1-month cessation group was also diagnosed with breast cancer. Vaginal bleeding was the most common adverse event in the cessation groups: 7 1-month and 6 2-months. There were 5 other adverse events (e.g., cataract, gastroenteritis) all within the 1 month cessation group.

There were a total of 198 clinical encounters across intervention arms ranging from 5 (among 3 women) for continued use, 64 (among 33 women) for 1-month, and129 (among 55 women) for 2-months cessation. The most common issues for the 1-month cessation group were the same for the 1- and 2-month cessation groups: hot flashes (n=14/n=36), sleep disturbances (n=10/n=22), night sweats (n=5/n=16) and headaches (n=8/n=10).

We measured compliance among the cessation group on the follow-up questionnaire: >85% of women were able to stay off their hormones as randomized, but there were differences by group: 7.1% were not in compliance in the 1-month group vs. 12.6% in the 2-month cessation group ($p<0.01$). Women in the 2-month cessation group reported greater difficulty staying off their hormones ($P<0.05$). The main reasons for noncompliance included just feeling better taking them (64.0%) managing night sweats (66.4%), hot flashes (70.8%), and sleep disturbances (66.3%).

Task D. Ascertain outcomes from mammograms (mammographic density and clinical interpretation)

The first reviews of mammograms for density and clinical assessment were completed in June 2005. Altogether the study radiologist assessed 1475 clinical mammograms on study participants and the Research Specialist entered information from the radiology assessment form into the mammogram database. The Research Specialist has also digitally scanned each study subject's baseline and follow-up mammograms for density determination. Recall rate was determined exclusively from the study radiologist's interpretation of the study mammograms, where recall was defined as any assessment requiring additional imaging or evaluation on either breast (BI-RADS assessment of 0).

We digitized the craniocaudal projection of the left breast from the index and study mammograms using a Kodak Lumysis 85 scanner. We used Cumulus software developed at the University of Toronto to measure percent breast density, breast area, and dense area measured per pixel.

Task E. Data quality and control

Questionnaires were scanned using Teleform technology that has built-in logic checks for the data. The radiologist fills out the Radiology Assessment form for each subject after completing reading the mammograms and the Research Specialist enters the form data into the mammogram database. The study programmer runs quality checks on those data monthly. The quality control digital images are being randomly selected, rescanned and re-read for density outcomes on an ongoing basis.

All mammographic breast density measures were read by the same trained reader in batches of 50 films. To reduce variability, a participant's index and study films were read in random order within the same batch of films. Each film was individually evaluated, with the reader blinded to participant identifiers, randomization group, and to the timing of the exam (index or study mammogram). To evaluate quality assurance, we included four inter-batch repeats and four intra-batch repeats within each batch.

We had complete study data including mammogram and both questionnaires for 95.5% of the 1477 women who remained in the study; but because of the differential withdrawal after randomization, there were different proportions of women who had completed assessments and were included in the primary analyses: 95.6 continued use; 83.9% 1-month cessation; and 79.5% 2-month cessation.

Task F. Final analyses and report writing

Analyses and preparation of manuscripts for publication have begun and will continue into 2009.

KEY RESEARCH ACCOMPLISHMENTS:

REPORTABLE OUTCOMES:

Recruitment of study subjects began in November 2004 and ended in September 2007. All participant activities were completed during January 2008. Manuscripts are being prepared for submission to peer-reviewed journals.

CONCLUSIONS:

Just over one in ten women were recalled for additional imaging (11.1%). There were important differences in recall rate by HT strata with ET having a lower rate (9.4%) compared with EPT (13.7%). The ordering of the recall rates across randomization groups were in the same order in the ET and EPT users, but were not ordered by continued use, 1 month cessation and 2 month cessation. In contrast to the recall findings, there were ordered decreases in percent density by randomization group for all women and when analyzed by HT type.

This study will prove to be important to understanding factors associated with women whose breast density changes when HRT is removed. We have learned from this study, that breast density can have clinically and statistically important declines and not have an ordered effect on recall rates. The data from this study has also provided important information about women who might be more amenable to stopping HRT, particularly among women who have been long-term users. There are several next-steps that we will be taking as a team. One of our highest priorities at this time is to collect the breast tissue of women in the trial who underwent a biopsy during the study period (at the time of this report, there have been 43 women who have experienced 63 breast biopsies). We are interested in collaborating with the University of California at San Francisco's Breast density program project to analyze the breast tissue based on changes in mammographic breast density after HT withdrawal. There are some critical scientific questions that will still be answered with this study population.

REFERENCES:

- Buist DSM, Newton KM, Reed S, Anderson ML, Aiello EA, King E, Palmer L, Seger, D. Can Short-Term Hormone Therapy Cessation Before Mammography Decrease Breast Density And Improve Mammography Performance? A Randomized Trial. Department of Defense's Era of Hope. June 8-11, 2005. Philadelphia, PA.

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